

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings of claims in the application:

**Listing of Claims:**

1. (Currently amended) A method of treating a tumor in a mammal, said method comprising delivering to said tumor a serum-stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion,

wherein said delivering is by injection at an injection site that is distal to said tumor in said mammal;

~~and~~ wherein said lipid portion of said nucleic-acid lipid particle comprises a cationic lipid, a neutral lipid, and a lipid conjugate that prevents aggregation during formulation;  
wherein cells of said tumor are responsive to said nucleic acid; and  
wherein cells of said tumor are transfectable by said nucleic acid.

2. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein said nucleic acid comprises an expressible gene.

3. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 2, wherein said expressible gene encodes a member selected from the group consisting of therapeutic polypeptides and therapeutic polynucleotides.

4. (Currently amended) A method of treating a tumor in a mammal in accordance with claim 2, wherein said gene is heterologous to a gene in the mammal.

5. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 3, wherein said gene is a member selected from the group consisting of genes encoding suicide enzymes, toxins and ribozymes.

6. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 2, wherein said gene encodes a member selected from the group consisting of herpes simplex virus thymidine kinase (HSV-TK), cytosine deaminase, xanthine-guaninephosphoribosyl transferase, purine nucleoside phosphorylase, cytochrome P450 2B1.

7. (Currently amended) A method of treating a tumor in a mammal in accordance with claim 2, wherein said gene is homologous to a gene in the mammal.

8. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 2, wherein said gene encodes a member selected from the group consisting of proto-oncogenes, cytokines, immune stimulatory proteins and anti-angiogenic proteins.

9. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 2, wherein said gene is a member selected from the group consisting of IL-2, IL-12, IL-15 and GM-CSF.

10. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 2, wherein a therapeutically effective amount of said gene is generated at said tumor.

11. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein said cationic lipid is a protonatable lipid having a pKa in the range of about 4 to about 11.

12. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 11, wherein said protonatable lipid is a member selected from the group consisting of DODAC, DODAP, DODMA, DOTAP, DOTMA, DC-Chol, DMRIE, DSDAC and mixtures thereof.

13. (Canceled)

14. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein said lipid conjugate is a member selected from the group consisting of PEG-lipids and PAO-lipids.

15. (Currently amended) A method of treating a tumor in a mammal in accordance with claim 13, wherein said lipid conjugate is reversibly associated with an outer

lipid monolayer, and wherein said lipid conjugate exchanges out of said outer lipid monolayer at a rate faster than that of PEG-CerC20.

16. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein said nucleic acid-lipid particle is substantially devoid of detergents and organic solvents.

17. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein a therapeutically effective amount of said nucleic acid-lipid particle accumulates at said tumor.

18. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein a therapeutic effect is detected at the site of said tumor.

19. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 17, wherein said therapeutically effective amount comprises greater than about 0.5% of an administered dose.

20. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein said nucleic acid-lipid particle has a diameter of about 50 nm to about 200 nm.

21. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 20, wherein said nucleic acid-lipid particle has a diameter of about 60 nm to about 130 nm.

22. (Currently amended) A method of treating a tumor in a mammal in accordance with claim 20, wherein ~~said~~ the nucleic acid-lipid particles are of a uniform size.

23. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein said nucleic acid-lipid particle has a nucleic acid to lipid ratio of greater than about 3 mg nucleic acid to mmole of lipid.

24. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 23, wherein said particle has a nucleic acid to lipid ratio of greater than about 14 mg nucleic acid to mmole of lipid.

25. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 23, wherein said particle has a nucleic acid to lipid ratio of greater than about 25 mg nucleic acid to mmole of lipid.

26. (Currently amended) A method of treating a tumor in a mammal in accordance with claim 1, wherein said nucleic acid remains at least 90% intact when said particle containing about 1  $\mu$ g DNA is treated *in vitro* with about 100 U DNase 1 in digestion buffer at 37°C for 30 min.

28. (Currently amended) A method of treating a tumor in a mammal in accordance with claim 1, wherein said ~~administering~~ delivering is performed at least once per eight weeks.

29. (Withdrawn) A method of sensitizing a neoplastic cell to a compound, said method comprising:

a) transfecting said neoplastic cell with a serum-stable nucleic acid-lipid particle encoding a gene-product comprising a nucleic acid that is fully encapsulated within a lipid, wherein administration of said nucleic acid-lipid particle is by injection at an injection site that is distal to said neoplastic cell; and

b) delivering to said cell a first compound which is processed by said gene-product into a second compound, wherein said cell is more sensitive to said second compound than said first compound.

30. (Withdrawn) A method of sensitizing a neoplastic cell in accordance with claim 29 wherein said first compound is formulated in a lipid.

31. (Withdrawn) A method of sensitizing a neoplastic cell in accordance with claim 29 wherein said gene product is a member selected from the group consisting of therapeutic polypeptides and therapeutic polynucleotides.

32. (Withdrawn) A method of sensitizing a neoplastic cell in accordance with claim 29 wherein said gene product is a member selected from the group consisting of suicide enzymes, toxins and ribozymes.

33. (Withdrawn) A method of sensitizing a neoplastic cell in accordance with claim 29 wherein said gene product is a member selected from the group consisting of herpes simplex virus thymidine kinase (HSV-TK), cytosine deaminase, xanthine-guaninephosphoribosyl transferase, purine nucleoside phosphorylase, cytochrome P450 2B1 and analogs thereof.

34. (Withdrawn) A method of sensitizing a neoplastic cell in accordance with claim 29 wherein a therapeutic effect is detected at the site of said neoplasia cell.

35. (Previously presented) A method of treating a tumor in a mammal, in accordance with claim 5, wherein said gene encodes a suicide enzyme and said method further comprises administering a prodrug.

36. (Canceled)

37. (Currently amended) A method of treating a tumor in a mammal in accordance with claim ~~36~~ 35, wherein said prodrug is administered after the serum-stable nucleic acid-lipid particle.

38. (Currently amended) A method of treating a tumor in a mammal in accordance with claim ~~36~~ 35, wherein said prodrug is administered before the serum-stable nucleic acid-lipid particle.

39. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 9, further comprising administering a chemotherapeutic agent.

40. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 39, wherein the chemotherapeutic agent is administered after the serum-stable nucleic acid-lipid particle.

41. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 39, wherein the chemotherapeutic agent is administered before the serum-stable nucleic acid-lipid particle.

42. (Canceled)

43. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein the cationic lipid is DODAC.

44. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein the neutral lipid is DOPE.

45. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein the lipid portion further comprises a PEG-lipid.

46. (Previously presented) A method of treating a tumor in a mammal in accordance with claim 1, wherein the lipid portion further comprises cholesterol.

47. (Previously presented) A method of treating a tumor in a mammal, said method comprising delivering to said tumor a serum-stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion,

wherein said delivering is by injection at an injection site that is distal to said tumor in said mammal; and

wherein said tumor is responsive to the gene product of the nucleic acid; and

wherein said nucleic-acid lipid particle comprises a cationic lipid, a neutral lipid, and a lipid conjugate that prevents aggregation during formulation.

48. (Previously presented) A method of treating a tumor in a mammal, said method comprising delivering to said tumor a serum-stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion,

wherein said delivering is by injection at an injection site that is distal to said tumor in said mammal;

wherein cells of said tumor are transfectable by said nucleic acid-lipid particle;  
and

and wherein said lipid portion of said nucleic-acid lipid particle comprises a cationic lipid, a neutral lipid, and a lipid conjugate that prevents aggregation during formulation.

49. (Previously presented) The method of claim 47, wherein said nucleic acid encodes a member selected from the group consisting of: suicide enzymes, toxins, tumor suppressor genes, and cytokines.

50. (Previously presented) The method of claim 47, wherein said nucleic acid encodes a suicide enzyme; and said method further comprises administering a prodrug.

51. (Previously presented) The method of claim 47, wherein said nucleic acid encodes a toxin.

52. (Previously presented) The method of claim 47, wherein said nucleic acid encodes a tumor suppressor protein.

53. (Previously presented) The method of claim 47, wherein said nucleic acid encodes a cytokine.

54. (Previously presented) The method of claim 50, wherein the suicide enzyme is a member selected from the group consisting of: HSV-TK, purine nucleoside phosphorylase, and cytosine deaminase.

55. (Previously presented) The method of claim 50, wherein the tumor is a melanoma.

56. (Previously presented) The method of claim 50, wherein the tumor is a colorectal tumor.

57. (Previously presented) The method of claim 50, wherein the tumor is a sarcoma.

58. (Previously presented) The method of claim 51, wherein the toxin is *Pseudomonas* exotoxin.

59. (Currently amended) The method of claim ~~51~~ 52, wherein the tumor suppressor protein is apoptin.

60. (Previously presented) The method of claim -53, wherein the cytokine is IL-12.

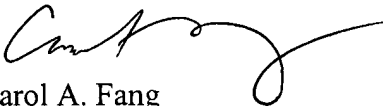
61. (Previously presented) The method of claim 51, wherein delivery of the serum-stable nucleic acid-lipid particle is intravenous.

### CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

  
Carol A. Fang  
Reg. No. 48,631

TOWNSEND and TOWNSEND and CREW LLP  
Two Embarcadero Center, 8<sup>th</sup> Floor  
San Francisco, California 94111-3834  
Tel: 415-576-0200  
Fax: 415-576-0300  
Attachments  
CAF:caf  
60194545 v1